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by

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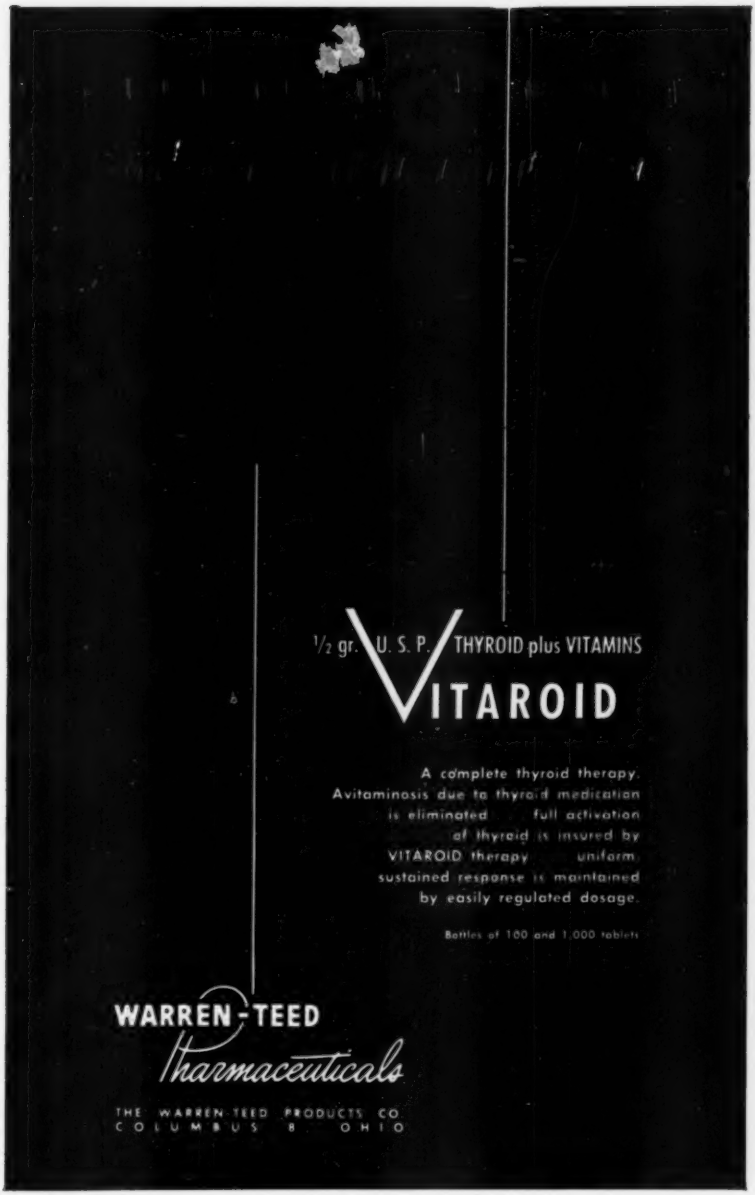
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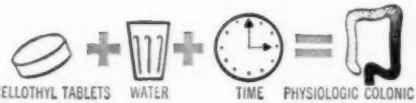

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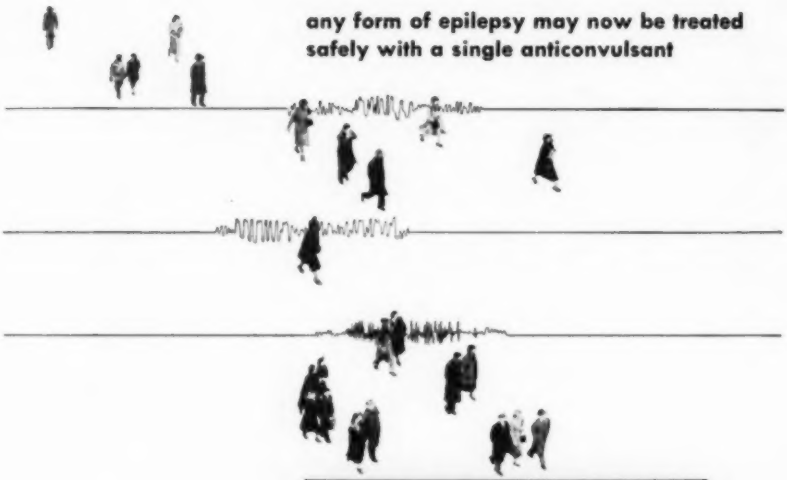

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BULLETIN OF
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COMPARISON OF TESTS OF THYROID FUNCTION*

JAMES HOWARD MEANS

Jackson Professor of Clinical Medicine, Harvard University, and Chief of the Medical Services, Massachusetts General Hospital, Boston.

DIAGNOSIS in the field of thyroidology should rest, as in other areas of clinical medicine, primarily upon history and the physical examination of the patient. Having accomplished that, however, the doctor then has the duty and privilege of resorting to various laboratory aids to diagnosis. This evening for a few moments I will dwell upon what use we can make of certain of such procedures in gaining more complete knowledge of the nature of the morbid process in our patients with thyroid disorders, or in aiding us in the ruling of thyroid disorders in or out, in differential diagnosis.

I shall concern myself with three tests—BMR (basal metabolic rate), PBI (protein bound iodine of the blood serum), and RAI (the uptake of radio actively labelled iodine by the thyroid gland). The diagnostic significance of these tests, either singly or in combination‡, is what I shall hope to clarify.

There are other procedures useful in the area under discussion, such as the determination of serum cholesterol, creatine tolerance, thyro-

* Read March 2, 1950 at the Stated Meeting of The New York Academy of Medicine.
From the Thyroid Clinic of the Massachusetts General Hospital, Boston.
‡ Having defined them, I shall in the remainder of the paper refer to the tests by these alphabetical designations.

tropin concentration in blood or urine, bone age, and others, but I have had relatively little experience with them and so shall not discuss them at this time. It is my belief also that the triad of tests which I first mentioned is the one on which chief dependence should be placed in estimating thyroid function for diagnostic purposes.

First let us consider, when we make any of the tests in question, precisely what it is that we are measuring: next, what significance measurement of this particular factor may have with respect to our diagnostic problem. BMR, PBI and RAI may all be accepted as in some degree tests of thyroid function, but they test different aspects of thyroid function, and therefore it should be clear that the question—which is the best of the lot—is irrelevant. What we really want to know is—what are the limitations of each?

BMR, the most venerable member of the triad, as ordinarily determined clinically, is nothing more than the determination of the amount of oxygen the subject takes up from the atmosphere per unit of time while in a state of physical, and if obtainable, mental rest, at normal room temperature, and eight or more hours after food. It is an index of how briskly the flame of life of the subject is burning at that particular moment. All activities of living animal tissue—protoplasm—eventually require oxygen. Even when a physiologic act takes place anaerobically an oxygen debt is acquired which must soon be paid off if the animal is to survive.

It is well known that the hormone of the thyroid importantly affects rate of bodily oxidation. Depriving the organism of thyroid by total thyroidectomy, or other destructive process, drops its oxidation rate by about 40 per cent. By feeding thyroid it can be raised even more than that. Ergo, BMR is a good index of thyroid function, but as we shall see presently, there are other factors than the secretory activity of the thyroid which can affect it. Moreover, what, one may ask, determines that portion of total respiratory metabolism, 60 per cent approximately, which takes place in the absence of the thyroid gland? This is an intriguing and fundamental question worthy of the attention of investigators, but perhaps not one which concerns us now as diagnosticians.

Having determined the basal oxygen absorption of an individual, we cannot use this information for diagnostic purposes without a suitable frame of reference. We cannot say the subject's metabolism is normal or abnormal without some method of comparing it with the

metabolism of subjects known to be normal. The commonly employed procedure is to relate metabolism to surface area, and for practical purposes this is probably adequate. There are, however, certain theoretical objections to it. Before surface area formulae were available, body weight was used, but there was more variation between subjects of widely different shapes—tall-leans or short-fats—when weight was used as the reference point than when area was the criterion.

But neither weight nor area takes into consideration the ratio in any given subject between actual living protoplasmic mass, which is what determines metabolism, and inert tissue material such as fat, extracellular fluid, etc., which is metabolically inactive. An index of protoplasmic mass would seem to be the ideal criterion, but how can one measure that?

Years ago (1914), my then collaborators, W. W. Palmer and J. L. Gamble and I,[1] attempted to solve this problem by relating BMR to endogenous creatinine elimination. We did find a significant correlation, but being then not sufficiently fundamental in our orientation, we abandoned the method in favor of the Du Bois height-weight formula[2] which appeared shortly afterward. In the late thirties (1936-38), N. B. Talbot and his collaborators,[3-5] took up BMR and creatinine elimination again, and found as did we, a good correlation, but they also failed to develop their findings further. I have always regretted that we did not exploit the method more thoroughly.

I must not at this time belabor the theoretical aspects of BMR determinations any further. I merely want to indicate that it is desirable that when the diagnostician makes these measurements, he stop to think a bit about the nature of the thing he is measuring. With regard to thyroidal activity it seems to me permissible to say that BMR can be accepted as an index of the total impact of thyroid hormone upon its end-organs—that is to say upon all the cells of the body. If the sensitivity of end-organs remains constant, BMR is an index of the amount of thyroid hormone delivered to end-organs.

PBI, the second member of the triad, presents a simpler problem. It can be safely accepted as a tolerably dependable index of the level of thyroid hormone circulating in the blood, of hormone on its way from factory (thyroid gland) to consumer (the target cells). The height of this stream obviously is related to the activity of the thyroid gland, but in a different way than is BMR. The two could, theoretically

at least, vary independently if a change should occur in the sensitivity of end-organs to thyroid hormone. It has been found also (Riggs[6]) that when the functional status of the thyroid gland changes rapidly, PBI parallels this change more promptly than does BMR. For example, what we call the Farquharson effect,[7] namely, the fall in cases of non-myxedematous hypometabolism when thyroid administration is stopped, to a level lower than the starting one, is more pronounced in the case of PBI than it is in that of BMR.

There is one important artefact that may intrude in PBI determination. The gall bladder dyes containing iodine hook into serum proteins and remain in the blood stream for months. They would be determined as PBI, and may cause an elevation of PBI which is not due to thyroxine. Indeed, if any patient has had cholecystography within a year, his PBI may not accurately reflect his blood level of thyroid hormone.

The last member of the triad, RAI, may be said to represent directly the thirstiness, or avidity, of the thyroid gland for iodine. It will be affected by the degree of stimulation of the thyroid, as for example, by its normal stimulator, the thyrotropic hormone of the pituitary, or thyrotropin, and by the capability of the gland to respond to stimulation. The latter can be affected by chemical agents which interfere with either the iodine trapping mechanism of thyroid cells or with the process of synthesis of thyroid hormone.

There are various methods of using labelled iodine for diagnostic purposes. One can give a so-called tracer dose of radiation and follow the uptake directly by Geiger counter over the gland, or one can collect urine and determine uptake by the thyroid indirectly on the assumption that the portion of the dose of radiation given which is not recovered in the urine is chiefly collected in the thyroid.[8] There are several variations of each of these approaches which I have not time to go into at present. One can if one wishes, follow RAI in thyroid gland, blood and urine simultaneously. Such studies are yielding some very comprehensive information on thyroid function. They are hardly at present, however, within the field of practical diagnosis.

I will now review certain formulae which have been obtained by this triad of tests in various types of thyroid disorders and in related conditions. In doing so I want to make it clear that I am not claiming that the use of all three tests has become mandatory for routine diagnostic purposes. PBI determinations are less available and more costly

than those of BMR, and RAI uptakes are far less accessible and far more costly than either of the others. Moreover, both PBI and RAI determinations require much more highly trained personnel than does the time-honored and generally used BMR determination.

My point is, however, that if the three, or any two of them, can be had, a somewhat greater insight into the patient's status can be obtained than with any one of them alone. Particularly is this true in differential diagnosis. We may draw analogies with the role of tests of liver function in liver disease, or of kidney function in kidney disease. You have a whole battery of tests for each, but certainly don't need them all for routine purposes. Yet if you want a really penetrating understanding of what is going on in the diseased liver or kidney, you must have information on more than one aspect of its function.

Let us now get down to cases and see what different combinations of the three measurements we find in various diseases.

In Tables 1 and 2, I have given diagnoses and have indicated by arrows whether we may expect the BMR, PBI and RAI to be normal, elevated or depressed in each of the several conditions shown. It should be said at once that the direction of some of the arrows is based on rather scanty data and subject to change without notice. I have avoided numerical values, but will remind you that BMR may get as low as −45 per cent in total athyreosis and as high as +80 per cent in thyrotoxicosis. According to the method our laboratory uses, PBI in euthyroidism runs from 3.5 to 7.0 micrograms per cent, and in clinical thyrotoxicosis from 8. to 35 micrograms per cent. In clinical hypothyroidism it runs from 3.0 to 0.0 micrograms per cent. RAI uptake in 48 hours, as we find it, runs in euthyroidism from 20 per cent to 55 per cent of the administered dose; in hyperthyroidism from 60 per cent up, and in hypothyroidism from 15 per cent down.

In Table 1 we have first the normal or euthyroid state. In this by definition the tests are all normal—the arrows horizontal and double ended. Next are shown the direction the tests take in clinically definite thyroid diseases. It will be seen that in all such the BMR and PBI arrows point in the same direction. In the thyrotoxic or hyperthyroid states they point upward, in the hypothyroid, downward. This is quite what is to be expected. The RAI arrow also takes the same direction as the others except in two situations. In thyrotoxicosis persistent on iodine, of course, BMR and PBI are elevated, because by definition it is a state

TABLE I

DIAGNOSIS	BMR	PBI (SERUM)	RAI (UPTAKE)
NORMAL OR EUTHYROID	⟷	⟷	⟷
THYROTOXICOSIS OF GRAVES' DISEASE	↑	↑	↑
THYROID ADENOMA WITH HYPERTHYROIDISM	↑	↑	↑
HYPERTHYROIDISM PERSISTING ON IODINE	↑	↑	↓
HYPERTHYROIDISM FACTITIA	↑	↑	↓
HYPEROPHTHALMOPATHIC GRAVES' WITH EUTHYROIDISM	⟷	⟷	⟷
PRIMARY MYXEDEMA	↓	↓	↓
PITUITARY MYXEDEMA	↓	↓	↓
IODINE WANT	⟷	⟷	↑
END-ORGAN INSENSITIVITY TO THYROID HORMONE (THEORETICAL)	↓	↑	?

when thyroid hyperfunction persists despite continuing treatment with iodine. However, if under such circumstances a tracer dose of RAI is given, very little will be taken up because the gland is already saturated with iodine. This same formula of BMR and PBI up, and RAI down, is found, so far as I know, only in one other condition, and in that it is close to pathognomonic. In thyrotoxicosis factitia, that is to say, thyrotoxicosis due to the ingestion of thyroid with or without doctor's orders, the BMR will be elevated because end-organs respond to an excess of hormone whether it be derived from the thyroid gland or the alimentary canal. PBI will be elevated in similar fashion. However, an excess of thyroid hormone in the blood suppresses the pituitary with respect to thyrotropin secretion, therefore in thyrotoxicosis factitia RAI uptake will be depressed. If you have a patient who is thyrotoxic, but with no goiter, no eye signs, and who denies taking thyroid, use the triad of tests and perhaps you can pin a diagnosis of thyrotoxicosis factitia on him by finding the formula BMR and PBI up and RAI down.[9]

In hyperophthalmopathic Graves' disease with euthyroidism the values of all three tests are normal.[10] Of those cases of Graves' in which the BMR swings to hypothyroid levels we have not as yet PBI and RAI data.

In primary thyroidal myxedema, as might be expected, all three values are down, and the same holds true in myxedema of pituitary origin, although the fall in PBI and RAI may be relatively less than that in BMR. I have indicated this in Table 1 by making the PBI and RAI arrows a little shorter.

In an endemic goiter area where iodine is scarce, the thyroid, by increasing its avidity for iodine maintains for a long time normal output of hormone, so that BMR and PBI would be normal, but if RAI is given, its uptake would be increased.

The last item in Table 1 is purely hypothetical. We have never established a diagnosis of insensitivity of end-organs to thyroid hormone. But such a condition may exist. It has been found in the case of parathyroids and gonads. It is well to be looking for it. What the test formula would be in such a condition, should it exist, is purely a matter for speculation. The BMR one might expect to be down, and if the thyroid gland attempted to compensate by overproduction of hormone, as in the castration phenomena, PBI and RAI would be up. But would the thyroid gland hyperfunction under such circumstances? Who can say?

At this point I can hear some of you murmuring—so what? Why bother with all this barrage of laboratory tests except in the rare case where one wishes to rule thyrotoxicosis factitia in or out? I will reply to that. Indeed there is no reason at all in clinically obvious cases. Any one of the tests is sufficient under such circumstances, or, if you are a good clinical observer, you can get on well without any of them. Symptoms and signs of the disease are sufficient in well developed cases. My reason for showering you with arrows, however, was to indicate the meaning of the different measurements so that they can really be helpful in borderline cases when diagnosis is not clear, and when you will get more help from two, or better three, of the tests than from one.

While BMR alone is what is generally relied on, as we shall see presently, there are several non-thyroid factors which may shift it up or down and make it difficult to interpret except when other evidence is available. In borderline hyper or hypothyroid situations, either PBI or RAI is more dependable as a diagnostic aid than BMR. There is some difference of opinion among authorities of which of the first two has the greater diagnostic significance in this connection. Of recent years we have not infrequently been able to establish a diagnosis of

TABLE 2

DIAGNOSIS	BMR	PBI (SERUM)	RAI UPTAKE
ANOREXIA NERVOSA	↓	↓	↓
STARVATION	↓	↓	↓
NON-MYXEDEMATOUS HYPOMETABOLISM	↓	⟷	⟷
HYPERMETABOLISM WITHOUT THYROTOXICOSIS	↑	⟷	⟷
DINITROPHENOL POISONING	↑	↓	⟷
NEPHROSIS	↓	↓	⟷
PREGNANCY	↑	↑	?
PHAEOCHROMOCYTOMA	↑	⟷	⟷
LEUKEMIA	↑	⟷	⟷
ADDISON'S DISEASE	↓	⟷	⟷

hyperthyroidism in persons with BMR within the standard range by finding significant elevations in either PBI, RAI or both.

In Table 2, I have shown the directional tendencies in certain non-thyroidal states which may enter into differential diagnosis. In anorexia nervosa and in starvation, the two states presumably being identical so far as endocrine balance goes, we get formulae quite like those in pituitary myxedema. In the last mentioned hypopituitarism results from actual destruction of the anterior lobe; in the others it is underactive, we believe from inanition.

Hypometabolism with no clinical evidence of thyroid disease, in our experience, has shown normal PBI and RAI. Just what these cases represent physiologically I don't know. It has been suggested that they are examples of end-organ insensitivity, but I do not find that hypothesis altogether convincing. Dr. Silver has been good enough to tell me of his observations on hypermetabolism without evidence of thyroid disease. They also show no alteration in PBI and RAI. I have included them in Table 2 and hope Dr. Silver will comment.

In Dinitrophenol poisoning there is a terrific elevation of metabolism which is clearly not related to thyroid function. Chaikoff et al[11] have found the RAI normal and the PBI depressed in rats. Why the latter,

is not clear. What the lowered BMR of nephrosis represents, I don't know. It is usually accompanied by lowered PBI, but a few observations do not show depression of RAI. Pregnancy is accompanied by a rise in BMR and in PBI. We have no observations in RAI in normal pregnant women. The situation here is to be regarded as a genuine increase in thyroid function. Physiological hyperthyroidism, so to speak.

The formula in pheochromocytoma is of great interest, and of much importance in differential diagnosis. In this condition there is no hyperthyroidism but there is hypermetabolism due to an excess of another calorigenic hormone, adrenaline. This raises BMR but not PBI or RAI.

A similar formula is to be found in leukemia, but the mechanism involved is more obscure. Finally, in Addison's disease there characteristically is lowering of BMR but not of PBI or RAI.

In conclusion I may say that after the diagnostic possibilities of history and physical examination in suspected thyroid cases have been exhausted, use may be made of any or all of the laboratory tests mentioned. At times they will add to the understanding of the case and clarify points in differential diagnosis in an outstanding manner. When we make use of them it is well that we bear in mind just what it is we are measuring, and what the special significance of the finding may be and the limitations of each of the several methods.

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THYROTROPIC EXOPHTHALMOS*

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THE demonstration of the production of exophthalmos by an anterior pituitary principle in animals, has served to explain several aspects and the extremely variable clinical appearance and course of this ocular disorder in man, when associated with thyroid dysfunction. The experimental studies of Smelser,[1-3] Pochin,[4] and Marine and Rosen,[5] indicated the existence of a different type of exophthalmos of Graves' disease with quite a different significance, viz., thyrotropic exophthalmos, as distinguished from thyrotoxic exophthalmos or that commonly associated with hyperthyroidism. Though the linkage may be incomplete, this newly separated type seems to correspond clinically precisely with those cases which showed after operation a progression, if not a malignant increase, in exophthalmos. With a different pathogenesis, diverse pathologic changes, and running a dissimilar course, this type requires different treatment, for indeed the choice of wrong therapeutic measures may lead to most unfortunate consequences.

The discovery of the thyrotropic hormone of the pituitary *marked* the beginning of our understanding of the interaction of the thyroid and the pituitary, on the production of a diversity of ocular complications, the most striking of which is exophthalmos. In his experiments, Smelser[1] showed that extracts of the anterior pituitary produce an extreme, forward displacement of the eyes in thyroidectomized guinea pigs, and that the exophthalmos persisted unchanged after death. In thyroidectomized animals which had the cervical sympathetic ganglion on one side removed in addition, injected extracts of ox anterior lobe pituitrin produced the proptosis of equal extent on both sides Thus, in this experiment, he eliminated the role of sympathetic stimulation as a cause of the displacement of the eyes. The effects of excess thyroxin or epinephrin in guinea pigs are entirely different.

In contradistinction to the exophthalmos of thyrotoxic goitre which

* Read at The Stated Meeting of The New York Academy of Medicine March 2, 1950.

is due mainly to sympathetic stimulation of muscle by adrenalin, when sensitized by an excess of thyroxin in the blood, a type of displacement which disappears on death, the *exophthalmos* of thyrotropic origin is real, viz., it is due to an increase in orbital content. A change in water balance produces edema of the tissues of the orbit, conjunctiva and lids. Round cell infiltration of muscles and lacrymal gland, and connective tissue hyperplasia and edema of the fat of the orbit occurs. Smelser estimated the constituents of the orbital contents of his animals to have increased 100 per cent in fat, 40 per cent in the dorsal lacrymal gland and 22 per cent in the extrinsic muscles. He found this connective tissue hyperplasia to have occurred also in other parts of the body where the fat is rich in connective tissue. Curtis[8] called attention to the fact that localized myxedema may follow surgical removal of a thyrotoxic gland. These histologic changes with rather more hypertrophy and fragmentation of the muscles, with late secondary fibrosis in long standing cases, have been confirmed in large part on human tissue.

The ocular and general signs of thyroid dysfunction depend upon the preponderance of action of the thyroid, or of the pituitary gland. Excess thyroxin with a minimum of anterior pituitrin produces the classic picture of hyperthyroidism with which every one is familiar.[7-9] The clinical appearance of a patient with excess anterior pituitrin (or thyroid-stimulating hormone) and with little, or an absence of thyroxin, may merit description. In these cases the basal metabolism may be very slightly raised, or normal, but is usually subnormal. Sympatheticotonia is absent. The eye signs are extreme and characteristic. In its pure form this entity is relatively uncommon and, as should be expected, mixed types are more frequent, viz., those which show some accompanying thyrotoxicity. Clinically one encounters the more frequent pure thyrotoxicosis on one hand, and, ranging through cases of diminishing thyrotoxicosis and increasing thyrotropism, cases of the less common, pure, thyrotropic variety on the other hand.

The eye signs offer the earliest and easiest means of differentiating these groups and it is these changes which frequently compel the patient to seek medical attention.[10]

The classic ocular and general signs of diffuse toxic goitre are well known. The widening of the interpalpebral fissure, the retraction and lagging of the upper eyelid and the infrequency of winking produce the staring expression and create the appearance of exophthalmos, which

may not be present in fact. The excursions of the eyes are not interfered with and exophthalmos, if present, is reducible on pressure. These eye findings are relieved, at least in part, by adequate reduction of the activity of the thyroid gland.

In thyrotropic exophthalmos the displacement of the eye appears early in the disease, is frequently unilateral, so that an orbital tumor is suspected, and is progressive.[11] Tearing, with edema of the eyelids and conjunctiva may appear early and may be severe. Redundancy of the bulbar conjunctiva with folds overlying the lower lids, or even prolapse, is common and suggestive. The excursions of the eyes are limited in all directions of gaze due to the histologic changes affecting all of the muscles of the affected eyes, causing the patient to complain of diplopia; thus, the name exophthalmic ophthalmoplegia is sometimes applied to this disorder. In the severe or malignant form, which may develop with amazing rapidity, especially after thyroidectomy, the eyes become extremely proptosed, solidly fixed in position, chemotic and with lids edematous and unable to cover the eyes. Exposure keratitis then develops, ulceration follows and loss of the eyes results. Treatment, therefore, must be prompt and effective.

In an effort to clarify the roles played by the thyroid and pituitary glands respectively in individual patients, excluding the pure thyrotoxic cases, Mann[12] classified her cases in three groups as follows:

Group 1: Primary deficiency of thyroxin with compensatory excess of thyrotropic hormone secretion. These cases showed the thyrotropic exophthalmos without thyrotoxic eye and general signs, and with thick coarse skin, rather suggesting myxedema.

Group 2: Primary excess thyroxin as initial symptom, followed by thyroid atrophy or removal, replaced by excess thyrotropic hormone. In these cases the initial symptoms were those characteristic of thyrotoxicosis, while the later signs were those produced by excess thyrotropic hormone. This is the type of case which every physician has seen following thyroidectomy, in which the exophthalmos increased to an alarming degree, frequently ending in loss of the eyes. The increase may follow the operation by a few weeks or it may require several years. Since malignant exophthalmos occurs disproportionately more frequently in men, in whom thyroid dysfunction is much less frequent than in women (1 case to 10), all cases in men should be carefully searched for evidence of the thyrotropic element.

It is this group that is of greatest interest to the surgeon, for he must be able to determine whether or not this most unfortunate complication will follow the treatment or removal of the thyroid gland. It may not be possible to predict in every case with assurance what might be expected to follow the operation. Sloan[13] has emphasized certain significant findings with which every physician, and certainly every surgeon, engaged in the treatment of thyroid dysfunction should be familiar.

Group 3: Excess thyroxin and excess thyrotropic hormone arising simultaneously. In this group of cases one observes both specific and infiltrative changes in the orbits. The classic eye signs of thyrotoxicosis may be observed in addition to edema of the eyelids and conjunctiva, solid proptosis, and impairment of motility of the eyeballs. The proper management of this group is as yet to be found. Thyroidectomy is prone to lead to malignant exophthalmos and must be avoided. Attention should be directed more toward suppressing the thyrotropic element rather than the thyrotoxic.

Treatment

The treatment of exophthalmos associated with thyroid dysfunction must be directed toward the underlying cause, the general manifestations of the disease and the management of the ocular complications. Our province in this presentation is especially concerned with the management of the ocular complications and the preservation of vision. Close coöperation between the surgeon, internist and ophthalmologist is called for and treatment of the eyes should be concerned more with prevention than with cure.

It is imperative that every surgeon be familiar with the ocular manifestations of thyroid disease. Not only because they indicate the proper course of treatment but also because blindness is a very real threat. In his interest in the preservation of sight, the ophthalmologist, in addition to the treatment carried out by the internist, may employ several local measures. The protection of the eye from exposure which leads to ulceration is his foremost consideration. The placing of intermarginal lid adhesions serves this end best but these must be placed before the tension of the eye and eyelids is too great. Such adhesions may be left as long as desired and severed at any time. Excision of the edematous conjunctiva, or removal of the tissue from the lids is not helpful. In extreme cases where intermarginal adhesions cannot be placed, orbital decompression

has to be resorted to. Naffziger's[14] intercranial method of removing the roofs of the orbits may be helpful. Other surgeons have advocated removal of the lateral walls of the orbits or depression of the floors into the antra. With proper medical care and prompt insertion of intermarginal adhesions this radical surgery may be avoided. The correction of diplopia, which may be the patient's leading ocular complaint may be extremely difficult, if not impossible. Surgical measures on the extraocular muscles themselves offer the best chance but this should be delayed until all signs of general activity have subsided. Spontaneous regression of the ocular complications may occur after some months or years and temporizing measures to preserve the eyes may be justified.

Summary

Sloan[13] has emphasized conservatism in cases manifesting thyrotropic disturbance. He especially mentioned cases showing exophthalmos out of proportion to the degree of hyperthyroidism as a bad prognostic sign. Asymmetric exophthalmos is frequently due to infiltrative changes and will increase after thyroidectomy. Diplopia, or ocular muscle paralyses indicate infiltrative orbital changes and should serve as a warning to the surgeon. The absence of a high basal metabolic rate should alert the physician to the predominance of the thyrotropic element. The overactivity of this anterior pituitary hormone is held in check by the excess of thyroxin. Reducing the thyroxin supply by operation or medical treatment may allow the thyrotropic hormone to run amuck to produce the distressing conditions known as malignant exophthalmos or exophthalmic ophthalmoplegia. Let the surgeon, therefore, beware of operating upon any patient showing these signs and if they should arise following operation, it is necessary to raise the metabolic rate to stop the progress of the disease. At the same time measures must be taken to safeguard vision.

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DIABETIC NEUROPATHY*

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THE neurologic complications of diabetes mellitus remain a matter of perennial interest. Although there is little really new to present at this time, a "present-status" report with particular attention to some of the contributions during the last 5 years may be useful. Some particular aspects of diabetic neuropathy—its relationship to other diabetic complications, the prominence in it of autonomic nerve disease, etc.—can well be re-emphasized. Finally, I should like to point out some of the unsolved, but solvable, problems that should be engaging our attention as investigators.

I can best illustrate the type of disease we are dealing with by quoting from a paper published in 1885 in the Lancet by F. W. Pavy.[1]

"I am perfectly satisfied that certain symptoms of disordered nerve action . . . are very apt to accompany diabetes. . . . A lady aged 48, whom I saw for the first time in 1871, and who had then been diabetic for ten years, presented no symptoms of nerve disorder till February, 1880. She then began to complain of pains in her limbs, and by April of that year she was decidedly ataxic. The usual account given by these patients of their condition is that they cannot feel properly in their legs, that their feet are numb, that their legs seem too heavy. . . . Darting or 'lightning' pains are often complained of. Or there may be hyperaesthesia, so that a mere pinching up of the skin gives rise to great pain; or, it might be, the patient is unable to bear the contact of the seam of a dress against the skin on account of the suffering it causes. Not unfrequently there is deep-seated pain, located, as the patient describes it, in the marrow of the bones, which are tender on being grasped; and I have noticed that these pains are generally worse at night. With this there is the usual loss or impairment of the patellar tendon reflex.

"Sometimes pains and manifestations of perverted sensibility are

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noticed without ataxia. It is not always the legs that are affected; the arms may suffer. . . . A gentleman I have seen has had nerve troubles in one arm. . . . His skin and flesh were tender and the bone was painful; there was, moreover, some wasting of the limb."

Dr. Pavy's description is a vivid account of what we recognize today as diabetic peripheral nerve disease.

To visualize the functional and anatomical types of nerve fibers involved in diabetic neuropathy the two common medical diseases with important neurologic complications, diabetes mellitus and pernicious anemia, serve as a useful contrast. In diabetic neuropathy pain and thermal paresthesias are prominent symptoms. Diabetes produces to a greater extent than any other disease a profound disturbance in the function of the autonomic nerves.[2-4] Pain and thermal sensibilities and autonomic functions are mediated by small caliber, poorly myelinated neurons. In pernicious anemia the large caliber heavily myelinated neurons conducting motion, position and vibratory sensibilities are affected early and selectively.[5] Pain is rarely a significant complaint. In pernicious anemia degeneration of the lateral and posterior columns of the spinal cord is notorious, leading to exaggeration of the tendon reflexes, clonus, spasticity, and abnormal plantar responses. This type of spinal cord involvement does not occur as a result of diabetes. Nor does the cerebral involvement occasionally seen as a neurologic manifestation of pernicious anemia with confusion, depression, or outright psychosis occur as a result of diabetes.[5]

The incidence of neuropathy in diabetics is probably about one in twenty.[2, 6, 7] Its relationship to the natural history of diabetes has been clarified in recent years by the study of the diabetic background of patients who develop this complication.[7-10] Joslin and Root[11] pointed out that, in nearly all instances, neurologic disease begins during periods of diabetic non-regulation. In a large group of patients studied later a few developed neurologic difficulties as the earliest symptom of the disease. In general, though, months or years of uncontrolled diabetes preceded the development of serious peripheral nerve disease. The bulk of patients had had no previous diabetic treatment at all or only poor treatment. The majority had lost considerable weight due to the uncontrolled disease. Over half of them, of interest in reference to the possible harmful effects of long continued hyperglycemia, had never had coma, acidosis, or ketonuria even at the height of diabetic non-

CHART I—SYMPTOMS OF DIABETIC NEUROPATHY

Paresthesias, shooting or burning pain, numbness, tingling, "cold" feelings.

Muscular weakness, aches, cramps, tenderness, foot drop, wrist drop, flaccid paralysis.

Symptoms fluctuate, are worst at night, following infections, lapses in treatment, and sometimes after start of treatment. Begin in lower extremities, ascend to trunk, involve arms distally.

Precipitating factors (in group of 125 patients):

U. R. I.	2	Toxic hyperthyroidism	2
Pneumonia	1	Diabetic acidosis	4
Influenza	4	Diabetic coma	6
Pyogenic infections	4	Operations	4

regulation. The nerve disease was found to occur at nearly any age, without there being evidence of immunity either early or late.[2]

The neuritic symptoms (Chart 1) were found to fluctuate in intensity, paralleling generally the course of the diabetes, becoming worse following infection, after lapses in therapy, and sometimes after the start of treatment. A number of incidents notorious for aggravating the diabetic status were observed to aggravate or precipitate the neurologic disease, especially in those with a poor background of control.

A high incidence of other diabetic complications was found in patients with neuropathy. In the scale of diabetic complications, peripheral nerve disease occurred as one of a middle group that we can call sub-acute (Chart 2). Susceptibility to infection was common and an unstable and often severe diabetes the rule. A third of our group had diabetic retinal disease and more than a quarter hepatomegaly.[2]

A few years ago we were very much puzzled as to the origin of some bizarre complaints in patients with diabetic nerve disease:—night sweats without evidence of infection or fever, intolerance to heat and cold, tachycardia with weakness and fainting spells, gastrointestinal disturbances of an unusual type,[12] and distressing genito-urinary symptoms. As our study progressed it became apparent that these patients had autonomic nerve disease to an extent that had not been previously recognized, and which in many clinical situations escapes recognition.

Orthostatic hypotension was one of the striking results of autonomic nerve disease observed in more than a dozen patients.[2] This rare type of physiologic abnormality is one in which the blood pressure

CHART 2—COMPLICATIONS OF DIABETES MELLITUS

Acute: Acidosis, coma.

Sub-acute (curable):

- Susceptibility to infection,
  - Cutaneous
  - Urinary tract
  - Pulmonary, especially tuberculosis
- Increasing severity and instability of the diabetes.
- Neuropathy.
- Retinopathy, early.
- Hepatomegaly.

Chronic (not curable):

- Retinopathy, advanced.
- Diabetic cataracts.
- Occlusive arterial disease.
- Renal disease (intercapillary glomerulosclerosis).

cannot be maintained when the individual stands upright. It has been associated with various diseases involving the sympathetic nervous system.[13] Characteristic symptoms included weakness with exertion, dizzy spells, "black-outs" or syncope when standing. The symptoms were aggravated by fatigue, dehydration, severe diarrhea, etc. The blood pressure taken with patients lying in the supine position was ordinarily normal, the pulse rapid. When standing the systolic pressure fell 50 or more mm. of mercury, the pulse at the wrist became very rapid, weak and sometimes imperceptible. As the blood pressure fell below 50 mm. or so of mercury syncope occurred. Some were able to carry on normal activities with upright blood pressures of only 60-70 mg. Hg. All of the patients had a uniform background of poorly treated diabetes of many years duration, and neuritic disease of some severity.[2] Diabetic neurologic disease has become the commonest cause on our medical services of orthostatic hypotension.

Why the normal circulatory adjustments fail to compensate for the effects of gravity in these and other patients has been an intriguing physiologic problem. Several patients with this disorder have been studied recently by Dr. John Hickam.[14] A low index of cardiac output was found in patients lying in the supine position. An excessive fall occurred as they were tilted to 60°. In spite of intensive study the exact

CHART 3—CLINICAL FINDINGS IN 30 PATIENTS WITH DIABETIC NEUROPATHY AND GASTROINTESTINAL SYMPTOMS

Impotence, atonic bladder (either or both)	18 cases
Diabetic retinopathy	16 cases
Orthostatic hypotension (drop of 50 mm. Hg. or more in systolic blood pressure)	8 cases
Hepatomegaly	6 cases
Gastrointestinal symptoms:	
Cramps, pain, borborygmi	22 cases
Anorexia	20 cases
Severe constipation	15 cases
Vomiting	13 cases
Fecal incontinence	8 cases
Diarrhea	7 cases
Alternating diarrhea and constipation	4 cases
Nocturnal diarrhea	3 cases

mechanism that becomes defunct in these patients and that is responsible for the circulatory abnormality is still in doubt.

Another manifestation of autonomic nerve disease in patients with diabetic neuropathy was disturbance in the motor function of the gastrointestinal tract. In our 125 patients over 60 per cent developed unusual gastrointestinal symptoms with diabetic neuropathy; 53 of them became severely constipated, and in 22 it was virtually intractable; 27 patients had alternating, recurrent or continuous diarrhea, often nocturnal;[15] 4 had, in addition, anorexia with nausea and vomiting. X-ray studies were subsequently undertaken in 30 patients with particular emphasis on gastric motility, gastric emptying and motor performance of the small intestine.[12] The gastrointestinal symptoms and co-existing diabetic complications in this group are shown in Chart 3.

While roentgenologic evidence of disturbed gastrointestinal function was less conspicuous than the clinical symptomatology would lead one to suspect, some degree of gastric retention, slow transit of barium through the jejunum and ileum, and segmentation of the barium column were fairly constant features. The abnormalities were greater in those with severe neuropathy and in those with the more pronounced intestinal symptoms.

The clinical symptoms and roentgenologic abnormalities in the

patients with diabetic neuropathy resembled in many ways those that followed vagotomy. The parasympatheticomimetic drug Urecholine was found to correct the motor abnormalities at least partially, and was useful in symptomatic treatment particularly in those with anorexia and gastric retention.

About 1 in 4 of our patients with diabetic nerve disease developed genito-urinary and sphincter disturbances. Most of them had gastro-intestinal disturbances as well (Chart 3). The major complaints in the male were impotence, symptoms mimicking prostatism and, in both sexes, urinary and fecal incontinence. Cystometric studies of the bladder showed a high incidence of atonic neurogenic paralyses.[2] Detailed studies of the vesical dysfunction and methods of urologic management have recently been published by Lich and Grant,[16] and Emmett, Daut and Sprague.[17] The potential usefulness of the parasympatheticomimetic drugs has been studied only to a limited extent.[3]

A whole gamut of neurologic abnormalities may be illustrated by a 22 year old male, an alumnus of eleven years of diabetes so poorly controlled that his growth was stunted. His right knee and left ankle had become painlessly swollen and deformed two years earlier. He complained of anorexia, inability to eat, and intolerance to heat and cold. On examination his pupils were miotic. They enlarged very little when shaded, showed no reaction or a slight dilatation to light, but did constrict on accommodation. Pin prick and light touch were blunted over his fingers. The right knee and left ankle reflex could not be obtained. Thermal sensibilities were lost below the L 3-4 level.

There was no history suggestive of syphilis and serologic tests on five different occasions were negative. The spinal fluid was normal on two occasions. Roentgen examination of the intestinal tract showed considerable gastric retention at 6 hours, segmentation and delay in transit in the small intestine. These motor abnormalities were corrected by the administration of 10-20 mg. of Urecholine by mouth.

The photographs reproduced in Fig. 1 were taken after he had been painted with iodine, dusted with starch, and heated until his body temperature had been elevated 1.5° C. The black areas show the extent of his sweat gland innervation. There was virtually no sweat response to body heating over his face, extremities, or lower trunk. In hot weather the area of sweat gland innervation over his back was constantly drenched.

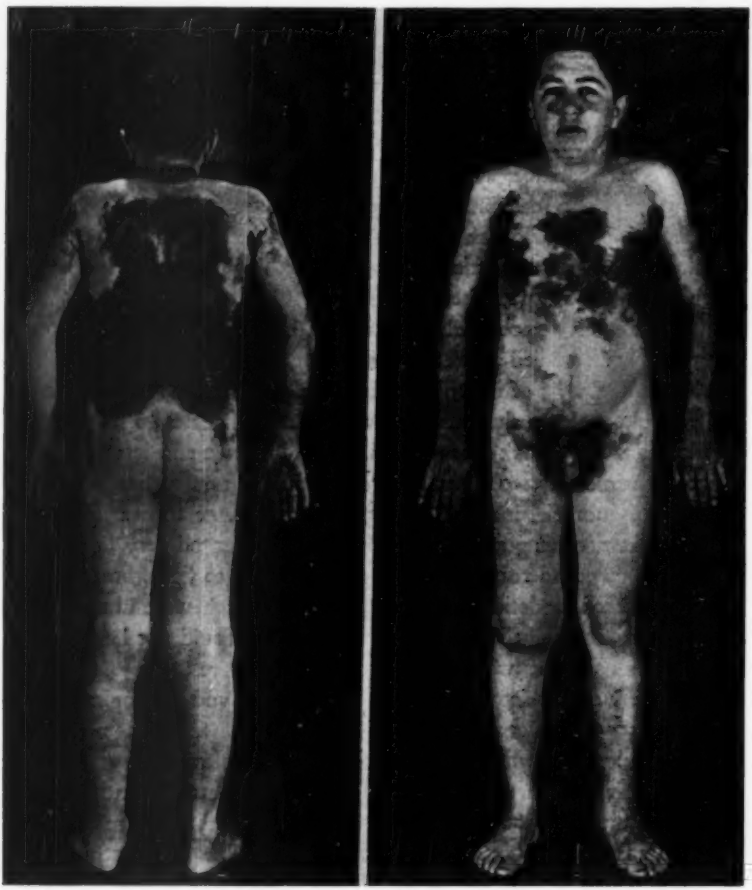

Fig. 1—Photographs showing area of sweat gland innervation, starch-iodine test, and neurotrophic disintegration of right knee and left ankle joints.

CHART 4—DIABETIC NEUROPATHY (NEURITIS)

1) *"Neuropathy":* Neuritic symptoms plus objective evidence of disease of peripheral nerves, persisting beyond any period of diabetic non-regulation.

Motor: Weak, tender, atrophic muscles.

Sensory: Areflexia, blunting of pain, thermal and touch sensibilities (motion, position, and vibration less affected).

Autonomic: Sweat secretion, pilomotor, vasomotor deficiencies; gastrointestinal and genitourinary disturbances.

2) *"Diabetic":* Related to natural history of diabetes:
Onset always during uncontrolled diabetes.
Made worse or better by factors influencing diabetes.
May become worse early in course of diabetic therapy.
Frequently associated with other diabetic complications.
Curable within limits only by diabetic therapy.

Over the dorsum of the left foot a scar was present where an infected ulcer persisted at one time for eight months. The right knee and left ankle were enlarged and deformed. X-ray examination of the knees showed bony proliferation, loose bodies and articular instability. Films of the left ankle showed similar bony changes typical of neurotrophic joint disintegration.[2, 8] He has now been followed for over three years. The right knee has become increasingly unstable and will probably require either fusion or amputation.

We have now come to the point where we can give a working definition of diabetic neuropathy (Chart 4). We have seen that it is a type of peripheral nerve disease, with sypmptoms and objective evidence of neurologic abnormality, in which there is a predilection for the involvement of small caliber neurons. Neuritic symptoms commonly occur in diabetics during periods of acidosis or ketonuria and subside promptly with diabetic regulation. The diagnosis of diabetic neuropathy should not be made unless evidence of disturbed nerve function persists well beyond any temporary period of non-regulation. As to the adjective "diabetic" we imply a definite relationship to the natural history of diabetes as already outlined. The diabetic etiology is confirmed by therapeutic experience. Successful treatment requires meticulous diabetic regulation over a period of weeks or months. No other type of therapy, physiotherapy, vitamin B injections, liver extract, vitamin B_{12}, etc., in my experience, has been of any definite value.[7, 10, 15, 18] In

patients with neurologic complications of recent onset, the prognosis is ordinarily good.[4, 6, 9] When the neurologic disease is of years' duration or complicated by such lesions as perforating ulcers or neurotrophic joint destruction,[19] the prognosis is, of course, poor.

Considering for a moment some unsolved problems, we are often asked what is the "pathology" of the nerve lesions in diabetes. While we are not lacking in confidence as to the validity of our functional studies and interpretations, we must admit that the morphologic aspects of the disease have received only fragmentary study. The technical problems involved in studying degenerative changes in poorly myelinated neurons are obvious. We would be looking for fibrils that were not there and that could presumably disappear leaving very little trace. Little is known about autonomic nerve pathology. Further pathologic investigations would be of great interest in instances of well-studied nerve disease.

Some have considered the neurologic complications of diabetes a result of vascular disease. Convincing pathologic studies, again, have not been made. Arteriography, study of blood flow by plethesmographic methods, etc. should bring out useful information.

It is frequently said that the "cause" of diabetic neuropathy, at least in metabolic or chemical terms, has not been discovered. The same can be said of all the complications associated with it clinically that result from chronic insulin deficiency. In addition to under-utilization of carbohydrate, excessive mobilization of fats and breakdown of proteins occur. Hypoalbuminemia seems to be characteristic and may reflect an inability of the body to manufacture the proteins necessary for tissue maintenance and repair.[18, 20, 21] As knowledge regarding the chemical effects of acute insulin deficiency progresses, the alterations that characterize the decompensated metabolism of diabetics with degenerative complications may be clarified.

The relationship of neurologic lesions in the extremities to the development of incapacitating foot infections is another important problem that has received too little attention. Perhaps a third or more of all foot infections in diabetics occur in those with neurologic disease. Neurologic factors are important not only in the development of perforating ulcers,[22] but in indolent infections, gangrene, traumatic blisters, etc. Effective therapy obviously requires an understanding of basic etiologic factors.

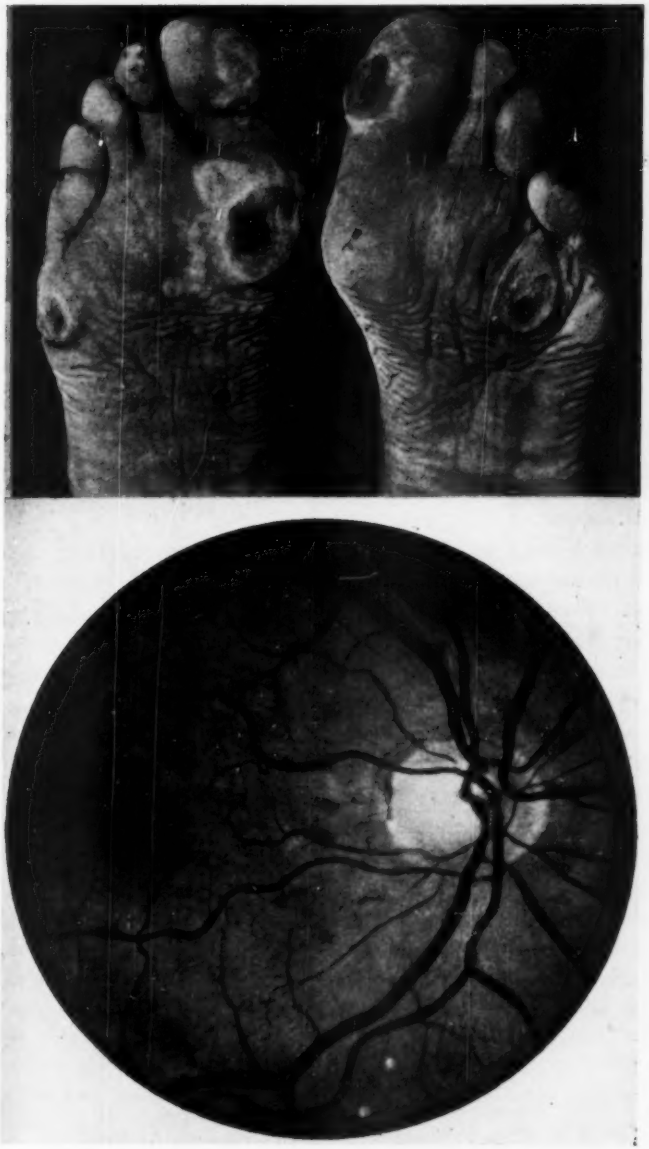

Fig. 2—Photographs (above) of chronic, ulcerated foot infections in a patient with diabetic peripheral nerve disease, and (below) punctate and superficial hemorrhages in retina, O. D.

The feet photographed in Fig 2 illustrate the problem. They belong to a 46 year old ship yard worker, who was admitted to our hospital in 1945, after having been disabled for eight months by chronic foot infections. He had developed diabetes eight years earlier and had symptoms of neurologic disease for one year. A toe had been amputated because of slow healing after trauma. After four months of neuritic symptoms he developed blisters about his toes that became infected. Healing was slow in spite of his being hospitalized for four weeks, and then resting 16 weeks at home. On examination he was thin and underweight. There were punctate hemorrhages in the optic fundi (Fig. 2). The skin over his lower extremities was thin, dry and shiny. There was no evidence of occlusive arterial disease. Neurologic examination showed unequal pupils, muscle weakness and atrophy in the legs, absent knee and ankle reflexes, and blunting of the cutaneous senses below the middle of the lower legs. Heavy glycosuria and ketonuria were present on admission to the hospital.

In the hospital he was kept in bed, the diabetes regulated, and the ulcers cleaned up. Healing was complete in a few weeks' time. He was able to resume work. In 1947 his diabetic regulation became lax again, neuritic symptoms reappeared, and further ulcers developed.

The relative importance of somatic and autonomic nerve disease, or other factors possibly responsible for the development of this type of foot infection is still uncertain. With careful diabetic regulation, prolonged bed rest if necessary, antibiotic therapy, local debridement and conservative surgery more infections are being healed and more feet saved for diabetic patients.[22]

One of the major objectives in the day by day management of diabetes is to prevent immediate and remote complications. We do not yet know what margin of safety we can assume for diabetic patients. Many of us have the conviction, though, that with the energetic use of presently available therapeutic methods we can prevent the bulk of the complications we have discussed from occurring.

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Discussions of Doctor Rundles' Paper

Foster Kennedy

War on disease is, indeed, not unlike war itself. For each to succeed one must have first, a plan of strategy, and second, sound tactics whereby the plan of strategy may be fulfilled. If the strategic conception be unsure or unsound, no matter how good the tactics, the result can hardly be fortunate. Strategy has to do with geography, topography, the disposition and placing of forces and the points at which best on such terms pressure on the enemy can be made. Tactics, that is to say, logistics, the transportation of troops from place to place (not necessarily the

right place for the carrying out of the grand design) may be developed so well, even though strategy be shaky, that success might come early, so that a war may seem about to be won by tactics, when suddenly it is found that tactics are not enough. I think it is something like this in the great war on diabetes. Our tactics have been extremely good. The introduction of insulin has saved millions of lives or at least prolonged millions of lives by the assumption that the origin of the disease lay in the islands of the pancreas. In the same way we have assumed that the neuropathies accompanying diabetes have been in the nature of a polyneuritis. On the contrary, I believe they are much more like what thirty years ago I called "neuronitis," that is to say, a degeneration not of the peripheral nerve only, but of the entire neurone. The charts shown tonight have demonstrated the existence of sphincter abnormality, sexual impotence and marked autonomic unbalance. These things do not occur as a result of mere peripheral nerve inadequacy. They are clearly the result of inadequacy in spinal roots, spinal cord and, I would suggest, of the autonomic system itself. It is by no means clear why peripheral nerves and radicals degenerate in the presence of diabetes. It has been said that they are the result of an ischemic neuritis due to a sclerosis of the blood vessels of the nerves. This has not been proven and is more a line of words than proven assertion in pathology. Certainly no such formula can account for the retinitis so often accompanying diabetes and I am sure that neuropathy often occurs in persons with very high blood sugar, in whom there is no spilling of sugar into the urine.

It would seem that one must look further back for causes of these conditions. One is reminded of the spinal cord changes called subacute sclerosis of the spinal cord occurring in the presence or *before* the presence of pernicious anemia. At first sight the anemia is a plausible reason for the occurrence of spinal sclerosis but more thought shows that both the anemia and the spinal sclerosis are due to the failure of gall bladder and liver function and the absence of hydrochloric acid in the stomach. So I put before this company the notion that diabetes and its neuropathies may not just be the result of disease in outlying functions such as the pancreas but may be due to a disorder in the balance of forces governed centrally in the nervous system. This is true of the stable maintenance of temperature; it is true of the stable maintenance of water balance. These are governed through the hypothalamus. If we

must look there for the causes of diabetes insipidus we had best raise our sights and look upwards perhaps to find the causes there of diabetes mellitus also.

MILTON B. HANDELSMAN

At the suggestion of the chairman, I shall introduce some physiological and biochemical considerations in this discussion of Dr. Rundles most thorough description of diabetic neuropathy. But first, we must reiterate the remarks of the first discussor, that we have a clearer definition of what diabetic neuropathy consists; we have a radiculo-myeloneuritis. It has been known since 1864 that diabetics complain of pains, weakness and numbness of various extremities but clinical descriptions have often been vague. Diabetes occurs in an age group where pains and aches commonly exist and diagnostic skill is needed to eliminate causes of complaints other than diabetes. These include many conditions that are commonly lumped together as "orthopedic causes," and include cervico-brachial syndrome, post-coronary left arm neuritis, bursitis, menopausal osteomalacia, low back syndrome with sciatica and humble flat-foot. We find in 1931 that Severinghaus recorded pain in 49 per cent of his diabetics while Wilder and Woltman found it in only 10 per cent of 2000 diabetics in the Mayo Clinic. Such and other varying statistical data demonstrate the need for rigid criteria in studies concerning the nature of diabetic neuropathy. We have mentioned some medical conditions that must first be ruled out; Dr. Rundles goes further in giving positive neurological findings that must be searched out when the diagnosis is to be made.

Those interested in diabetes are always interested in the question: how does diabetes cause or aggravate the sequelae. Again, we must say that the gap between physiological knowledge and clinical findings has not been overcome. It is a well established fact that neurones and nerve fibers depend on both glycolysis and oxygen utilization. This is somewhat different than in muscle physiology where function can go on for awhile in the absence of oxygen. The effect of anoxia on the nervous system is well known.

There is another significant difference, namely, that nerve survival and action are intimately associated with an electrical potential which

closely correlates with activity. As one nerve physiologist states: the electrical potential of a nerve is like the ticking of a clock—namely, the measurable outward phenomenon of an intricate system. The nerve potential has been carefully studied by neurophysiologists and has been shown to be due to changes in polarization along the neuronal surfaces. The cause of these progressive changes in polarization along the nerve has had many explanations. One, by Nachmanson has been most thoroughly studied; it attributes to the synthesis and breakdown of acetylcholine along the surface of the nerve the cause and biochemical groundwork. This worker has shown that the release and breakdown of acetylcholine is associated with alterations in the nerve membranes which break down the membrane resistance so that electrical impulses travel along the nerve. He has shown in electric organs that the voltage produced is proportional to the cholinesterase activity.

The connecting link of this system to glycolytic activity is through ATP and creatine phosphate which supply the energy to resynthesize acetylcholine. As in muscle, the utilization of carbohydrates supplies the energy to resynthesize the ATP, etc. Carbohydrate metabolism winds up the clock, so to speak. Although Nachmanson's work emphasizes acetylcholine as the *final* step in nerve activity, there is in the background an intensely complicated *biochemical* system involving glycolysis and all the related ancillary factors: the vitamin B components acting as coenzymes and metallic ions, sodium, potassium, calcium, magnesium, etc., which are also involved with the enzymatic reactions. Gerard, in fact, states, "I do not see how we can reasonably select one system from all this welter and just assign to it an essential role in conducting the nerve impulse." This neurophysiologist emphasizes ion action in the nerve and believes that the cause of the flow of electrons (viz nerve potential) is due to local changes in ion concentration at the molecular surface of the nerve cell.

Turning from the laboratory aspects to the clinical, we find that in diabetic neuropathy similar factors have been blamed, namely: improper carbohydrate metabolism, a vitamin lack, or changes in ionic balance. Dr. Rundles has described the fully developed syndrome. It is in the cases with earlier nerve involvement that we should look for clues concerning the etiology of diabetic nerve changes. For this, the classical classification of diabetic nerve involvement which has been studied clinically by many authors can serve.

1. Treusch in Wilder's Clinic has defined a group which he called "diabetes with pain." This applies to severe pain and paresthesias seen in diabetics who are completely decompensated, particularly in those with impending acidosis or in youngsters with acute onset of diabetes before treatment. There are usually few neurological signs and the condition is rapidly reversible with treatment. The Mayo Clinic workers attribute this condition to the derangement of mineral and water metabolism occurring during a decompensated diabetic state and point out that improvement comes rapidly after the establishment of normal salt and fluid balance. This emphasizes the "ion aspects" of nerve pathological physiology. Jordon reporting from the Joslin group calls this type "hyperglycaemic neuritis" and believes that the hyperglycaemia is the cause.

2. We have "neuritis following insulin therapy." This problem was first brought to general attention by Sydenstricker and his co-workers who showed that avitaminosis, notably pellagra, can be precipitated by insulin therapy. Similarly, diabetic neuritic pain can often be found in patients after insulin therapy has been started. In Dr. Rundles' monograph, one of his cases with severe neuropathy showed the first manifestations with insulin therapy. Sydenstricker believed that better utilization of carbohydrates stimulated by insulin therapy also led to the utilization of thiamin and other vitamins as *coenzymes*, thus creating a vitamin deficiency to the general organism. This seems to emphasize the role of vitamin deficiency as an etiologic agent.

A *third* grouping may be entitled "objective signs of nerve involvement in diabetics." Naunyn in 1898 considered the absence of the prepatellar reflex in diabetics as separate from the general problem of neuropathy and reviewed the vast literature that had been collected at that time. These observations made in the pre-insulin era are extremely interesting. The prepatellar reflexes could not be elicited in 20 to 30 per cent of all diabetics. Although they were more frequently absent in severe diabetics, a large percentage of severe cases retained it even during episodes of acidosis. Many patients with absent knee reflexes were followed for years without ever developing subjective or other objective symptoms of neuritis. With treatment, the reflexes returned in many patients. Recent observations are confirmatory of some of these facts. Severinghaus (1931) found reduced reflexes in 57 per cent and Jordon (1936) found that 45 per cent had diminished or absent patellar re-

flexes. More recently, interest has shifted from this reflex to a more sensitive measurement, namely, the determination of the vibratory sense. Collins and his coworkers (1946) found that "impairment in vibratory sense occurs in almost 90 per cent of diabetics and is present as frequently and almost as severely in diabetics without symptoms of neuritis as it does in those with symptoms." Barach (1947) also found that the vibratory threshold levels for diabetics were lower than for non-diabetics. Collins has found that the administration of large amounts of vitamin B has effected marked improvement in their patients; Barach finds that improvement of diabetic control and general nutrition are the chief influences in bringing about an improvement in the vibratory sensation.

There is a *fourth*, the last, grouping to be discussed, namely, "ischaemic neuritis." It is platitudinous to state that a great number of diabetics have peripheral vascular disease. Wilder has shown that the pathological picture found in the nerves of diabetics with severe resting or nocturnal pain and with the peripheral vascular disease is the same as that found in patients with other vascular disease such as thromboangiitis obliterans. Pure vascular neuritis probably exists in some diabetics and should be recognized, however, in view of the widespread disease often found in diabetics in the *smaller* blood vessels such as in the eye or the kidney glomerulus, as well as those larger elastic leg and coronary arteries, the role of ischaemia in diabetics needs further exploration.

Dr. Rundles has given us a picture of diabetic neuropathy with widespread ramifications. The clinician can no longer be satisfied by calling every pain in a diabetic patient a neuritis; we must look for all the ramifications. Are the 4 groups mentioned above early stages of diabetic neuropathy? Are they etiological factors in a reversible stage? What are the respective roles of ions, vitamins and blood sugar in producing diabetic neuropathy? Dr. Rundles has established definitely that deranged carbohydrate metabolism is at fault. How? Closing a discussion concerning a "degenerative" complication of diabetes by asking questions is a very orthodox procedure in the present state of knowledge.

[DISCUSSIONS CONTINUED ON NEXT PAGE]

FREDERICK W. WILLIAMS

I wish at the outset to compliment Dr. Rundles on his very excellent study and presentation of this extremely important complication of diabetes, one which has been to a great extent overlooked and neglected in recent years in the treatment of the disease. Briefly, I wish to emphasize again what Dr. Rundles has stressed: that neuritis in diabetics has diffuse or disseminate manifestations—it may be not only a simple peripheral neuritis of the extremities, but also gastrointestinal, genito-urinary, and cardiovascular neuritis. These last three are the ones which have, for the most part, been overlooked. We should constantly bear them in mind. We will find many if we look for them.

The neuritis of the extremities is the one which has been of greatest interest to me, personally. I wish to call attention to a few features which I regard, clinically important.

First, let us consider the onset. We all have seen and are well aware of the peripheral neuritis which is associated, as Dr. Rundles has pointed out, with long-standing, neglected diabetes. This is a stubborn condition to treat, and the important treatment is good, adequate diet with insulin for assurance of nourishment. We all use supplemental vitamin B therapy, but only rarely is the response rapid and dramatic. Rather, these patients slowly regain strength in their legs and the reflexes often are permanently gone. Then, there are the cases which develop rather rapidly. These, in my experience, are usually the ones which have a rather acutely developed and intense diabetes, with all of the cardinal symptoms, together with the neuropathy.

In my opinion the development of the neuropathy seems in some way related to the speed or acuteness of the disturbance in metabolism. This appears to be borne out by another type of case, in which the neuritic syndrome develops very soon after the patient has been in acidosis and dehydration, and has been rigorously treated and again restored to what we call "control." It would seem that the speed of these metabolic alterations has some bearing on the neuropathy. The explanation has been offered that this is due to changes in water balance and concomitant disturbance in ratio of the water soluble vitamins, especially B. This is only part, or one step in the process, since these cases are slow in response to vitamin therapy, even when it is pushed in doseage.

Finally, I wish to call attention to one other feature of neuropathy

in diabetics, which I have considered of vital significance, but which has not been adequately explored. This is the neuropathy of the extremities and the trophic changes resulting. Dr. Rundles touched on this in his observation of osteoporosis. We have carefully studied the lesions of the extremities in diabetics for a long time. We have gone to great length to classify these lesions on a basis of vascular impairment together with the presence or absence of infection. We have, for some time, been observing the extremities, trying to estimate the degree of neurotrophic changes that are present. We are all well aware of the vulnerability of the tissue, even in non-diabetics, in a case of transverse myelitis. Gangrenous pressure sores are common. The same neurotrophic factor may be contributing, in some measure, to the production of gangrene in lesions of the diabetic extremity. The problem is further complicated by the fact that the nerve pathology may be metabolic, or it may be avitaminosis, or it may be due to nerve ischemia on a sclerotic basis. These are the problems that still challenge us. Let us hope that further studies such as Dr. Rundles' will bring us ultimately to the solution and a sound therapy.

ADVANCES IN THE DIAGNOSIS OF BACTERIAL INFECTIONS*

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OBVIOUSLY, the presentation should not be and could not possibly be a systematic survey of methods used in diagnosis of bacterial diseases. In the first place it is not the objective of the Fortnight to give detailed technical accounts which are readily found in excellent texts. Secondly, the time available does not allow a point by point discussion of diagnosis of all known bacterial diseases.

It may serve a good purpose, however, to outline the general principles involved in bacteriological diagnosis and to present certain specific facts relative to the diagnosis of those bacterial diseases which are of immediate interest to the clinicians in this section of the country. Moreover, the selection of the material must be guided by the shifting of interests which is taking place under the impact of modern chemotherapy.

Diagnosis of bacterial diseases may be made directly and indirectly. Direct diagnosis implies the finding and isolation of the microörganism involved. Once the microörganism is isolated there remains the task of identification and characterization. The clinician is sometimes bored by the attempts of the bacteriologist to attach names, groups, subgroups, strain symbols, etc., to the microörganism isolated and may consider them to be of purely academic interest. Quite contrary, the characterization as complete as possible is of great practical importance for correct interpretation of the clinical significance of the findings. There are many methods used for the characterization of the organisms isolated. It should be emphasized that not all the methods can be necessarily applied to the identification of each microörganism studied. The methods may be summarized as follows:

Morphology in spreads of materials from the body and in cultures.

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Cultural and biochemical characteristics: Appearance of growth in media: Oxygen, CO_2 and nutritional requirements. Effect upon blood. Production of acids, alkalies, indole and other substances. Effect upon proteins, carbohydrates, and fats. Oxidation and reduction of dyes. Fermentation of sugars. Resistance to physical and chemical agents, i.e., heat, various salt concentrations and other substances.

Immunological identification: Study of whole antigens and protein and carbohydrate fractions.

Pathogenicity tests in animals of live microörganisms and toxins. Identification based on type of lesions and protection by specific immune sera.

The laboratory characterization of bacteria isolated is not sufficient for the evaluation of their pathogenic role in man. The division of bacteria into saprophytes and pathogens is arbitrary, since the ability of a microörganism to produce disease not only depends on its own biology but also on the site of invasion and the factors of susceptibility or resistance of the body. Knowledge of natural indigenous regional flora is helpful in the interpretation of pathogenicity of organisms found and must be reviewed shortly. Thus, the normal flora of the skin invariably consists of staphylococcus and quite often of Corynebacterium acnes. Occasionally, other microörganisms may be found which also present difficulties in interpretation unless they are isolated repeatedly from the cutaneous lesion. Surprisingly, few microörganisms are found in the nasal cultures of normal persons, although staphylococci and diphtheroides are normally present. The evaluation of the flora of the mouth and pharynx is indeed a very difficult matter. The basic flora consists of streptococci, mainly of the viridans group, Neisseria, diphtheroides, lactobacilli, and other microörganisms which are difficult or impossible to cultivate, such as fusiform bacilli and varieties of spirilla and spirocheta. In addition, potential pathogens may be harbored without producing infections, namely pneumococci, hemolytic streptococci, influenza bacilli, meningococci and Corynebacterium diphtheriae. In absence of an active infection these individuals may be grouped as carriers. Actinomyces is also frequently found in absence of infection. The alimentary tract flora varies in the different parts of the intestine. The empty stomach is usually sterile due to acidity. In certain diseases the flora may be abundant and variable. It is important to recall that tubercle bacilli, histoplasma and saprophytic acid-fast bacteria survive in the

TABLE I—MAJOR CRITERIA FOR SUBDIVISION

	Temperature		*Growth*		
	10° C	45° C	6.5% NaCl. 0.1% M.B. pH 9.6	Strong reduction	NH_3
pyogenic group	—	—	—	—	—
viridans	—	+	—	—	—
enterococcus	+	+	+	+	+
lactic group	+	—	intermediate between viridans and enterococcus		+

stomach. The upper part of the small intestine contains few bacteria, the only ones found are staphylococci and fecal streptococci. The flora of the lower part is extremely varied and abundant. The main microörganisms are of the colon-aerogenes group, fecal streptococci, yeasts, clostridia and bacteroides. The urethra usually contains staphylococci and diphtheroides. The vulva and preputium show Mycobacterium smegmatis. The flora of normal vagina differs before puberty and after menopause from that of the child-bearing period when lactobacilli predominate. Blood, cerebrospinal fluid, urine, tissues, serous fluids and bile are sterile in health.

When isolation fails, or when confirmation is needed as to the etiological role of the bacteria isolated, the indirect diagnosis is made by the demonstration of antibodies in the patient. They may be demonstrated in patient's serum in the form of agglutinins, precipitins and complement fixing antibodies and in patient's skin by the use of skin tests.

In passing over to the consideration of individual groups of microörganisms, the *Streptococci* need our greatest attention in view of their ubiquity, wide range of pathogenicity and great epidemiological significance. The remarkable progress achieved recently has been made possible by a variety of methods. Streptococci as a whole may be divided into the following main groups:

1. *Pyogenic group*—including all pathogenic and most of the hemolytic streptococci.

2. *Viridans group*—characteristic parasites of the human mouth and throat; and other forms.
3. *The lactic group*—saprophytes especially in milk (viridans and non-hemolytic).
4. *Enterococcus*—streptococci of fecal origin (hemolytic, viridans and non-hemolytic).

The above division into the main groups is made on the basis of certain major criteria, summarized in Table I.

There is no time to describe all the major groups. I shall limit myself to a brief discussion of the advances made in the studies on those groups which are of greatest interest to the clinician.

In the *pyogenic* group the most important members, the hemolytic streptococci have been studied immunologically in great detail, the impetus having been given by the important work of Lancefield. The hemolytic streptococci may be subdivided on the basis of specific carbohydrates, polysaccharide C which is an integral part of the cell. The C substances differ in streptococci of human origin (groups A, D, F, G, H, and K) and animal origin (groups C, D, E, L, M, and N.) Group A is the most important human pathogen, although some animal groups may be also pathogenic to man. At least 40 types have been identified in group A. Antigens M and T are responsible for the specificity of these types. M antigen is a protein apparently located near or at the surface of the cell, since enzymatic digestion may remove it without killing the cell. Interestingly, the M substance is responsible for virulence, since strains lacking M are avirulent. It is claimed that immunity to infection is correlated with type specific anti-M antibody. The support to this contention is found in the fact that in the absence of antibiotic therapy, recurrent naso-pharyngeal infections are never produced by the same type. Prompt penicillin therapy is likely to prevent antibody formation, with recurrent infections produced by the same type. The other type specific component, antigen T, is also a protein, free from nucleic acid, and confers no immunity to infection. There are other products elaborated by hemolytic streptococci which have been studied extensively, namely, fibrinolysins or streptokinase of Tillett and Garner, hemolysins of two types, S and O, hyaluronidase and erythrogenic toxins. They all are of great interest in connection with problems of pathogenicity, epidemiology and etiology of certain diseases. Their routine use for diagnosis is, however, not sufficiently established to

TABLE II—STREPTOCOCCUS s.b.e.

	s.b.e.	*Salivarius*
inulin	AG	—
arginine hydrolysis	+	—
40% bile	+	—
mucoid growth on 5% sucrose	—	+
synthesis of slime	+	—

justify a complete survey.

If this lecture were given a few years ago, it would have been necessary to give a complete description of the clinical and pathological implications of isolation of hemolytic streptococci from the patient, in view of their high virulence, and the variety of infections they are able to produce. Modern antibiotic therapy in Streptococcus hemolyticus infections is so remarkable that this aspect has lost most of its interest to the clinician. The remaining major divisions of streptococci, the *viridans* and *enterococcus*, deserve serious consideration of clinical bacteriologists for two reasons. Considerable progress has been recently made in their diagnosis and characterization, especially in connection with the streptococcus of subacute bacterial endocarditis. Furthermore, the effect of antibiotics is not nearly as uniformly dramatic as with Streptococcus hemolyticus and, therefore, their characterization is therapeutically important. Until recently, all the attempts to identify the Streptococcus viridans found in the majority of cases of subacute bacterial endocarditis were thought to be an impossible task. The contributions of Hehre and Neill, Loewe, Niven, Sherman, Washburn and White made it possible by the combined characterization on the basis of biochemical properties, resistance to physical and chemical agents and serological studies. Table II gives the major characteristics of Streptococcus s.b.e.

The studies were confirmed by Schneierson in our laboratory on 34 strains isolated from 32 cases. It should not be implied, that all streptococci isolated from subacute bacterial endocarditis belong to this group. There is no valid statistical information as yet on the incidence of the Streptococcus s.b.e. in subacute bacterial endocarditis. Obviously, there

TABLE III—ANTIGENIC STRUCTURE OF SOME OF THE MORE COMMON ENTERIC ORGANISMS

Group	Type	O Antigens	H Antigens	
			Phase 1	Phase 2
A	S. paratyphosa	(I), II, XII	a	.....
B	S. schottmuelleri	(I), IV, (V), XII	b	1, 2
	S. typhimurium	(I), IV, (V), XII	i	1, 2, 3
C_1	S. hirschfeldii	VI_1, VI_2, VII, (Vi)	c	1, 5
	S. choleraesuis	VI_1, VII,	c	1, 5
	S. oranienburg	VI_1, VI_2, VII	m, t	.....
	S. montevideo	VI_1, VII	g, m, s	.....
C_2	S. newport	VI_1, VIII	e, h	1, 2, 3
D	S. typhosa	IX, XII, (Vi)	d	.....
	S. enteritidis	(I), IX, XII	g, m	.....
	S. gallinarum	IX, XII	.....	.....
	S. pullorum	IX, XII	.....	.....
E	S. anatum	III, X, XXVI	e, h	1, 6

( ) indicate that antigen may be absent.

Taken with permission from Chapter 17, by H. R. Morgan, "Bacterial and Mycotic Infections of Man," edited by R. J. Dubos.

are other streptococci, with the exception of Streptococcus hemolyticus, and many other microörganisms encountered in this disease. With the improvements in the technique, the isolation of a wide variety of organisms has become possible, namely, para-influenza, brucella, salmonella, bacteroides, Streptobacillus moniliformis, Spirillum minus, actinomyces, gonococcus, diphtheroides and others.

In our laboratory, for a period of some twenty years we used a blood culture technique with the following features: The blood cultures are always made at the bedside. A large amount of blood, rarely less than 22 cc. is obtained. A series of fluid and solid media variously enriched is inoculated and incubated aerobically, anaerobically and under CO_2. The incubation period is at least four days and when required considerably longer. Daily smears and subcultures are made from aerobic media and at longer intervals of time from the remaining ones. The technique gives a high percentage of positive cultures and allows the isolation of

rather unusual organisms. Repeated blood cultures are made in order to exclude contaminants and organisms occasionally found in debilitating non-infectious diseases.

Among the microörganisms commonly known as the "*enteric group*" there exist many groups of vast clinical importance capable of producing a variety of pathological lesions, gastroenteritis being the most prominent manifestation. It is estimated that in twenty-one states there were 700,000 cases in 1934-1937. In view of the great number of subgroups and strains the studies on the *Salmonella* group are indeed complex. Progress in diagnosis of salmonella has been made through painstaking antigenic analysis. Briefly, the analysis is based on the occurrence of various antigenic components in the body of the bacillus, the somatic antigens called O and the flagellar antigens, called H. Salmonella are divided on the basis of the O antigens into groups. The groups are further subdivided into species on the basis of differences in H antigens. A single species may contain 2 types of H antigens, each one may predominate. One type is the specific phase, or phase 1 and the other is the group phase or phase 2. Either may contain more than one antigenic component. Table III summarizes the serological grouping.

A useful classification is also based on the pathogenicity of salmonella to men and animals, as follows:

1st Group: Primary human pathogens.

S. typhosa, S. paratyphi, S. schottmuelleri, S. hirschfeldii.

Common in U. S.: typhosa, schottmuelleri.

Rare in U. S.: S. paratyphi (A).

Rare in U. S. Common in Eastern Europe and Asia: S. hirschfeldii.

2nd Group: Primary animal pathogens, may be pathogenic for man—majority of salmonella.

Common in U. S.: S. typhimurium, S. cholera suis, S. enteriditis, S. panama, S. anatum.

3rd Group: Pathogenic only to animals, although more and more reported in man.

S. gallinarium most important member.

In a study on 1,100 cases of salmonella infections, excluding typhoid fever, Seligman reports the following clinical manifestations. Gastroenteritis occurred in 65 per cent of cases. The symptoms ranged from mild and feverless to high fever, prostration, dehydration and death. Dysentery with blood and slime occurred usually in young children.

There were some cases of recurrent episodes of chronic and ulcerative colitis. In the absence of other localization, the blood cultures were negative. In some instances the cases were confused with appendicitis and cholecystitis. S. typhimurium was the most common organism. Others were S. schottmülleri, cholerae suis, Orienienburg, enteritidis and anatis. Other localizations of the infection were meningitis, endocarditis, pulmonary lesions, osteomyelitis, parametritis, cholecystitis, pyelonephritis, appendicitis, and various abscesses in the intestinal tract, cervix and the abdominal wall. Some patients developed typhoid-like symptoms with bradycardia, rose spots and spleen tumor. It is important to bear in mind that children under ten accounted for some 40 per cent of all cases.

While S. typhimurium and enteriditis are predominantly found in gastroenteritis, S. cholerae suis is the most frequent cause of sepsis and other localizations which may occur in complete absence of gastrointestinal symptoms.

The most reliable method of diagnosis of salmonella infections, including typhoid fever, is the isolation of the organism. This is not always possible, the diagnosis then being made by the agglutination tests on patient's serum. Unfortunately, interpretation of agglutination with patient serum is difficult in some instances and cannot be subjected to hard and fast criteria. One should take into consideration natural agglutinins due to frequency distribution of organisms among the healthy population, percentage of carriers in the population, occupations relating to handling of meats and animals, and other sanitary factors differing geographically. It is possible to state, that generally a titer of 1:50 for H agglutinins and 1:100 for O agglutinins in absence of previous infection, observed during the first 10 days of infection may be regarded as a strong presumptive test for typhoid or paratyphoid infection. Recourse should be made, however, to repeated widals. In the course of the infection the titers usually follow a curve. In interpreting such a curve it is to be remembered that the rise in the curve is much more significant than the fall. For this reason it is important to make repeated tests in the first 3 weeks of the infection. It is also diagnostically significant when the rise is followed by a steep drop during the stage of convalescence. When the curve is studied in a previously vaccinated patient the base line will not be zero but at a level representing the residual titer due to inoculation. Now let us take cases in which sufficiently high O titers

TABLE IV—PRIMARY CLASSIFICATION OF THE MEMBERS OF THE GENUS SHIGELLA

	GROUP I *Lactose-negative* *Mannitol-negative*	*GROUP II* *Lactose-negative* *Mannitol-positive*	*GROUP III* *Lactose-negative* *Mannitol-negative*	*GROUP IV* *Lactose-negative* *Mannitol-positive*
True dysentery bacilli	S. dysenteriae S. schmitzii	S. paradysenteriae		S. sonnei
Allied species	S. ambigua S. minutissima S. septicaemiae	S. alkalescens S. gallinarum	S. gintottensis	S. equirulis S. ceylonensis B S. madampensis

were obtained to satisfy the criteria for diagnosis of an active enteric infection. In view of the fact that typhoid and paratyphoid A and B share a common O antigen, a high titer for the O antigens of typhoid and paratyphoid may appear simultaneously. On the other hand, the H agglutinins have a greater specificity. The O agglutinins serve to establish the diagnosis of an active infection more reliably than H agglutinins, since O agglutinins are not likely to persist following previous vaccination or past infection, while the H agglutinins may persist for a long time. But we must depend on H agglutinins for differential diagnosis between typhoid and paratyphoid infections.

The next clinically important group is that of *shigella*. The essential difference between salmonella and shigella is that the latter is not spread by animals but man. Convalescent and carrier states are the chief reservoir. In shigella infections gastroenteritis is the predominant involvement with few other localizations. There is no sepsis and no biliary tract infections. Joint involvement occasionally seen is a part of the gastrointestinal syndrome. We have seen, however, cases of urinary tract infections in the absence of gastrointestinal symptoms. The diagnosis is based mostly on isolation of the organism, since the diagnostic value of agglutination tests is doubtful. Attempts to isolate the organism should be made as early as possible on a number of differential media. The material should be fresh. Hardy introduced the use of a rectal swab which is very helpful. It may be of advantage to make smears of stools for the study of cells. Predominant polys suggest bacillary dysentery, while mononuclear cells suggest colitis of protozoan origin.

The important subgroups of shigella differentiated by biochemical and serological tests are given in Table IV.

Although identification of the groups of shigella are of great importance to the medical bacteriologist from the epidemiological point of view, little is known concerning the pathogenicity in man. The groups common in this country differ only in respect to severity of outbreaks, other clinical features being very similar.

In addition to salmonella and shigella there are also three other groups which may be responsible for outbreaks of dysentery, namely, the paracolon group, proteus and pseudomonas (B. pyocyaneus of previous terminology). The paracolon group consist of a long series of heterogenous organisms which lie taxonomically between E. coli and salmonella. Some strains were definitely shown to cause gastroenteritis outbreaks. Of special interest are recent studies of Bray and Beavan reported a year ago. They describe 10 epidemics of diarrhea of the new born, in which the predominant flora consisted of a strain of E. coli, clearly identified serologically. Normally the E. coli flora is greatly variable consisting of many different serological groups. In the epidemics described, it is indeed a remarkable fact that the normal strains of E. coli were consistently replaced by a single serologically homogenous strain, called E. coli var. Neapolitanum. The diarrhea of the new born is rather complex etiologically. There are apparently gastroenteric infections of the new born and young children caused by a variety of etiological agents, including viruses. E. coli var. Neapolitanum gives a high mortality rate, and occurs in association with warm weather. S. sonnei infection is usually characterized by blood and pus in the feces occurring in older children. Furthermore, there are diarrheas including neonatal infection distinguished by no special features and diarrheas caused by a virus, the presence of which is detected by its ability to produce infection in calves, as recently described by Baker and Light and Hodes.

Serious attention must be paid by the clinical bacteriologist and the clinician to diagnosis of *Brucellosis*. There are three types of brucella differentiated culturally and serologically, namely, Br. melitensis, Br. abortus and Br. suis. The cultivation and isolation is not an easy matter and requires special media. Differences in CO_2 requirements and resistance to certain bacteriostatic dyes, pyronin and thionin and other tests give presumptive differentiation. The identification rests with the study

TABLE V—REQUIREMENTS OF X AND V FACTORS IN GENUS HEMOPHILUS

	Required		
	X	*V*	*X and V needs not proven*
H. influenzae	+	+	H. pertussis
H. Koch Weeks	+	+	H. parapertussis
H. parainfluenzae	0	+	Moraxilla lacunata (H. duplex)
H. hemolyticus	+	+ or 0	H. ducreyi
H. suis	?	?	
H. hemoglobinophilus	+	0	

Taken with permission from Chapter 23, by H. E. Alexander, "Bacterial and Mycotic Infections of Man," edited by R. J. Dubos.

of the antigens. There are two main antigenic groups. One includes abortus and suis and the other melitensis. Cross absorption of agglutinins gives final identification.

Diagnosis can be of course unquestionably established by isolating the organism from the patient but this can be accomplished only in a relatively small percentage of cases and in the early stages of the disease. The protean manifestation of the disease and its occurrence in atypical, chronic and latent forms make it imperative to obtain a complete understanding of the diagnostic significance of indirect laboratory procedures. These are agglutination tests with patient's serum, skin tests and the opsono-phagocytic reaction. In an extensive study of 28 cases of chronic brucellosis as compared to several hundred cases of other infections, Evans and Robinson came to the following conclusions. No single test other than isolation can be relied on for diagnosis in a given case. Negative agglutination reaction cannot be used for exclusion of the disease. A positive agglutination reaction is evidence of infection. Titer 1:40 or higher occurs about 11 times as frequently in chronic brucellosis as in other illnesses. The higher the titer, the greater is the diagnostic significance. A positive skin test occurs only four times more frequently in chronic brucellosis than in other maladies. It is therefore, less reliable than agglutination and only suggestive of infection. Opsono-phagocytic reaction is the least reliable since it occurs only

twice as frequently in brucellosis as in other infections. Opsono-phagocytic reaction and skin tests add weight to a positive agglutination. The combination of all three positive reactions occurs about 10 times as frequently in chronic brucellosis as in other diseases.

Hemophilus group represented by H. influenzae is of considerable significance to the clinician in view of the high pathogenicity to man. The methods of diagnosis have recently advanced due to studies by Pittman, Goebel, Alexander, Dingle, Fothergill, MacPherson and others. Interesting nutritional requirements of the group help the identification of individual members. As may be seen from Table V, organisms may require for their growth the so called X-factor which is hemoglobin or hemin, and V-factor which is coenzyme I or II. Nicotinamide nucleotide may also serve as the V-factor. In addition they can be divided into encapsulated and non-encapsulated groups.

The encapsulated ones are divided into six serological types, a, b, c, d, e, and f. They are pathogenic to man and occur in meningitis, type B being predominant, in purulent arthritis and in obstructive infection of the lower respiratory tract. The latter syndrome first described by Lemierre represents an infection in which pharyngo-laryngeal symptoms are first to appear. Positive blood cultures are obtained from the onset and may persist even during convalescence. The onset may simulate croup. Later the infection spreads to the pleuro-pulmonary region and joints. Other localizations may be in the meninges, middle ear, conjunctiva and endocardium. Acute splenic tumor and cutaneous manifestations are less frequent.

The *non-encapsulated* H. influenzae occur preferentially in young children, although miscellaneous infections are also seen in the adult, namely pneumonia with bacteremia, occasional meningitis, and subacute bacterial endocarditis, in particular. The young person is definitely more susceptible to the non-encapsulated variety than the adult.

In making bacteriological diagnosis examination of smears from pathological fluids, spinal, synovial and pleural, is of particular importance. The forms are usually gram-negative and coccobacillary, simulating diplococci. If the stain is not satisfactory they may be confused with pneumococci. On further search it is almost always possible to find long thin and shorter thicker bacillary forms. Once the presence of the organism is suspected, the final identification of the encapsulated members can be made very promptly by the use of the so-called sero-

logical "Quellung" reaction with specific antisera. The identification of the non-encapsulated members is more difficult but it can be done by determining nutritional requirements and studying other cultural and biochemical characteristics.

My discussion of diagnosis of *diphtheria* will be brief since the standard methods are well known. During the past fifteen to twenty years numerous reports appeared in the European literature describing singularly severe outbreaks of diphtheria in which antitoxin proved of little value, so much so that a controversy started on the value of antitoxic therapy in this disease in general. The evidence for the value of antitoxic serum as a therapeutic agent is overwhelmingly convincing in most cases. The failures observed are due to the existence of certain types of diphtheria which behave differently from the usual type of the disease. The unusual types noted in the past fifteen to twenty years have the following characteristics in common:

In order to be effective in these cases, the serum must be administered within the first twenty-four hours of onset. There are two more aspects, namely, a shift in incidence from the age group one to five years to school children from six to above fourteen years old and diminishing incidence of laryngeal diphtheria, which in part may be due to the shift in age incidence. These clinical and epidemiological variations find a partial explanation in a comparatively new finding that there exist different varieties of diphtheria bacilli, namely, *gravis*, *intermedius* and *mitis*. The types are distinguished by their morphology, appearance of growth, fermentation of glycogen, pathogenicity for guinea pigs and antigenic homogeneity or diversity. The mitis type has many groups, the intermedius is antigenically homogenous, while the gravis has two main antigenic groups.

Pathology of diphtheria types should be briefly mentioned. The gravis type shows a tendency to damage underlying tissues in the local area of infection, tonsils and cervical lymph nodes. There is also correlation between the extent of local necrosis and necrosis in the malpighian corpuscles. In the *mitis* type the underlying tissues are normal and the reaction is mainly an abundant fibrinous exudate with extension of the membrane to the larynx and bronchial tree. There is little evidence of invasion of underlying tissues by bacilli of the gravis type, the assumption being that the necrosis in this type is due to stronger toxin. This conforms with the universal experience that mitis strains are associated

TABLE VI—CLINICAL SEVERITY OF 3 TYPES OF C. DIPHTHERIAE

	Hemorrhagic Phenomenon	*Paralytic Phenomenon*	*Laryngeal Involvement*
Gravis		More common than in other 2	
Mitis	rare	Less common	4 times more common than in other 2
Intermedius	More common than in gravis		

TABLE VII—DISTRIBUTION AND DEATH RATES OF 3 TYPES OF C. DIPHTHERIAE IN 25,000 PATIENTS

	Incidence	*Death Rate*
Gravis	44.5%	8.1%
Intermedius	26%	2.6%
Mitis	26%	7.2%
Atypical	3%	

with obstructive lesions of the air passages. Comparison of clinical severity, distribution and death rates are summarized in Tables VI and VII.

The old view that diphtheria is a toxic disease with the organism localized near the portal of entry is essentially correct. Recent work, however, has shown that diphtheria may spread hematogenously to internal organs. The organism was isolated by Graetz from 51 out of 76 fatal cases from internal organs. Twenty-six showed intermedius, while 25 were the gravis type.

Post-diphtheritic paralysis presents diagnostic difficulties which can be only solved bacteriologically when the laboratory is successful in recovering the etiological agent. Later on, when the preceding history is unknown or obscured there remains the differential diagnosis between this disease, infectious and toxic polyneuritis of unknown etiologies and the so-called Guillain-Barré syndrome.

Both in diphtheria and the Guillain-Barré syndrome the cerebrospinal

fluid shows an increased protein level without cells. More rarely this may be also seen in other forms of infectious polyneuritis of unknown etiology. The differentiation between the Guillain-Barré syndrome and post-diphtheritic paralysis must then be made clinically. Post-diphtheritic paralysis usually shows an early local paralysis of the palate and paralysis of accommodation, while facial paralysis is uncommon.

For the sake of brevity, I shall have to group together clinically important organisms which are totally unrelated bacteriologically but which have one feature in common, namely, that the portal of entry is predominantly in the upper respiratory tract. Our knowledge of their biology is rather limited. Their isolation and especially identification are not infrequently a challenge to the bacteriologist.

The greatest confusion probably exists in connection with *Actinomyces*. The old subdivision into human and bovine types does not hold and should be disregarded.

The division of actinomyces on the basis of gram stain and oxygen requirements has also proven misleading. Both characteristics are variable and cannot be clearly correlated, as previously thought, with their clinical significance.

Also in contrast to previous belief, there is no evidence that the disease is transmitted from cattle to man. Man is carrier of the organisms, which are frequently found in the mouth without causing any disease. Some unrecognized factors are necessary for induction of an infection.

The diagnosis rests on combined microscopic demonstration in the tissues, isolation of the agent and clinical signs.

The diagnostic importance of microscopic examination of smears of materials obtained from the lesion and sections of biopsy tissue cannot be overemphasized. Actinomyces and actinobacilli Lignieri have the property of producing in tissues aggregates, known as sulfur granules. On crushing, actinomyces appear in the form of gram-positive branching fiilaments, while actinobacilli yield short gram-negative rods.

Agglutination, complement fixation and skin tests are unsatisfactory.

In addition to actinomyces, miscellaneous filamentous forms, the *Leptothrichia* may be encountered in the sputum and mouth lesions. They are gram-positve and fail to show any branching. The evidence for their pathogenicity is not convincing.

The clinical manifestations of actinomycosis are generally well known. In this connection it may be of interest to mention that the literature has a record of 68 cases of actinomycosis of the heart. The involvement of the heart with resulting endocarditis represents invasion by contiguity by way of the pleural cavity and pericardium and also hematogenous invasion from distant foci. In endocarditis cases it is frequently possible to isolate the organisms from the blood.

Histoplasmosis is a disease recently studied very extensively in view of its clinical importance and difficulties it may present in differential diagnosis. The disease may be generalized involving all viscera or localized in a single organ. A generalized involvement of lymph nodes may be confused with Hodgkin's disease. The course may be acute and fatal or protracted with subsequent recovery. In the latter form the differentiation from tuberculosis is of special importance in view of the frequent occurrence of pulmonary calcified lesions.

As usual, the isolation of the organism is the most important means of diagnosis. Histoplasma capsulatum is a morphologically distinct fungus producing yeast-like forms at 37°C and mycelia at room temperature or 37°C. The organisms may be isolated by culture or animal inoculation of sputum, gastric washings, blood, bone marrow and biopsy tissue. The isolation is made easier when the contaminants are killed by addition of streptomycin and penicillin.

For indirect methods of diagnosis skin tests and complement fixation tests may be employed. According to Bunnell and others, skin tests are of greatest value. The test with histoplasmin should be accompanied by tests with tuberculin for exclusion of tuberculosis, and blastomycin, since blastomyces is an antigen immunologically related to histoplasma. The diagnostic dilution of histoplasmin is determined by previous titration in infected animals. The reading of skin tests should be done in 48 hours. A reaction with induration measuring 5 mm. is considered positive.

Complement fixation tests carried out quantitatively with histoplasmin and blastomycin may be also of diagnostic value.

Finally, your attention should be also drawn to a great variety of *non-spore bearing anaerobic organisms* which may be pyogenic and necrotizing and responsible for acute and chronic localized and generalized severe lesions and sepsis. Their possible role must be borne in mind when other organisms are excluded. Special methods must be

applied for their isolation which not infrequently may prove quite difficult. They may be grouped, as follows:

I *Bacteroides*, gram-negative bacilli: fusiformis, fragilis, funduliformis, and melaninogenicum.

II *Anaerobic staphylococci:* Micrococcus aerogenes, Micrococcus anaerobius and others.

III *Anaerobic streptococci:* foetidus, putridus, parvulus, and many others.

IV *Veillonella:* gram-negative cocci.

In conclusion I would like to point out that with the advent of modern chemotherapy, clinical bacteriology is bound to undergo many changes. Some procedures only recently considered important such as serological grouping of pneumococcus, meningococcus and the like, went sufficiently into oblivion to justify their complete omission from this presentation. In contrast, other aspects of clinical bacteriology continually grow in importance for with the development of new antibiotics chemotherapy cannot be employed successfully unless the etiological agent is isolated and the most potent drug is selected for clinical use by pre-testing of the organism in the laboratory.

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"Of 428 cases [of seasonal rhinitis and perennial rhinitis of allergic origin], 60% to 76% were benefited."

NOTE: A table, listing the results obtained in hay fever, shows that Hydryllin was used by ninety-seven patients and that 73 per cent experienced from 50 to 100 per cent benefit.

Gay, L. N.; Landau, S. W.; Carliner, P. E.; Davidson, N. S.; Furstenberg, F. F.; Herman, N. B.; Nelson, W. H.; Parsons, J. W., and Winkenwerder, W. W.: Comparative Study of Antihistamine Substances: III. Clinical Observations. Bull. Johns Hopkins Hospital 83:356 (Oct.) 1948.

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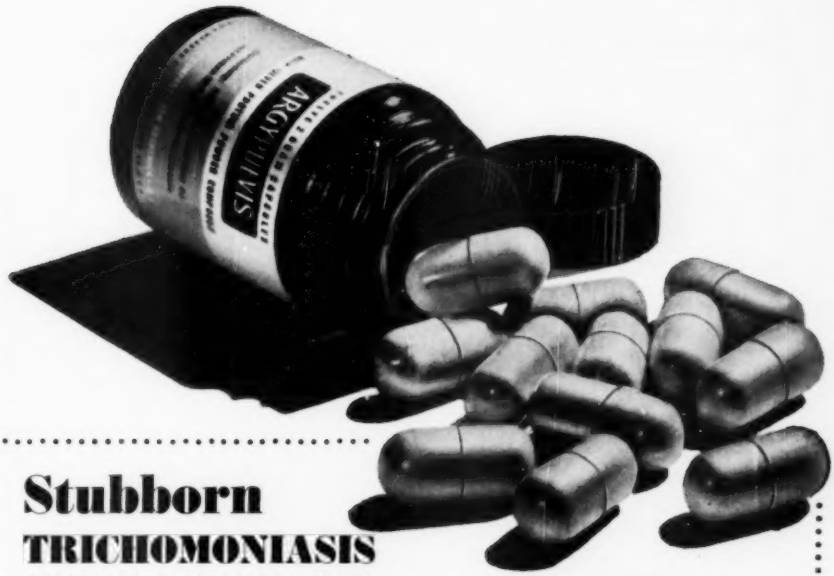

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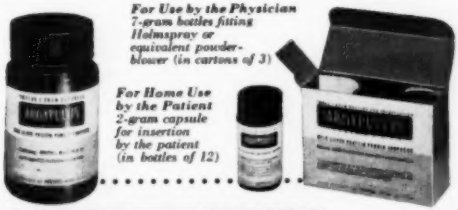

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1. Lehr, D.: Scientific Exhibit, Atlantic City Session, American Medical Association, June 6-10, 1949.

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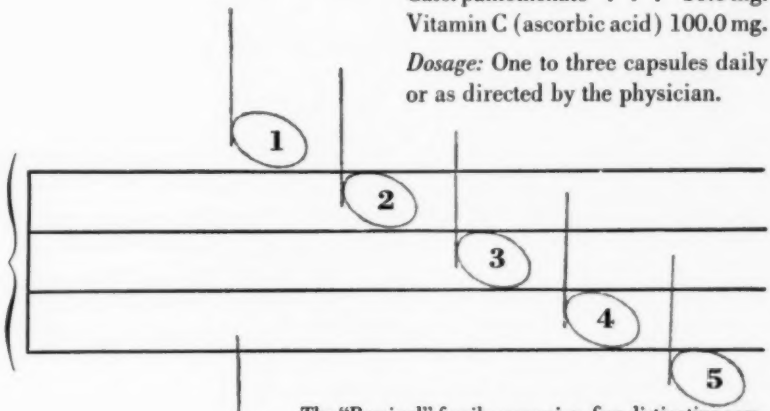

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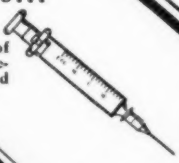

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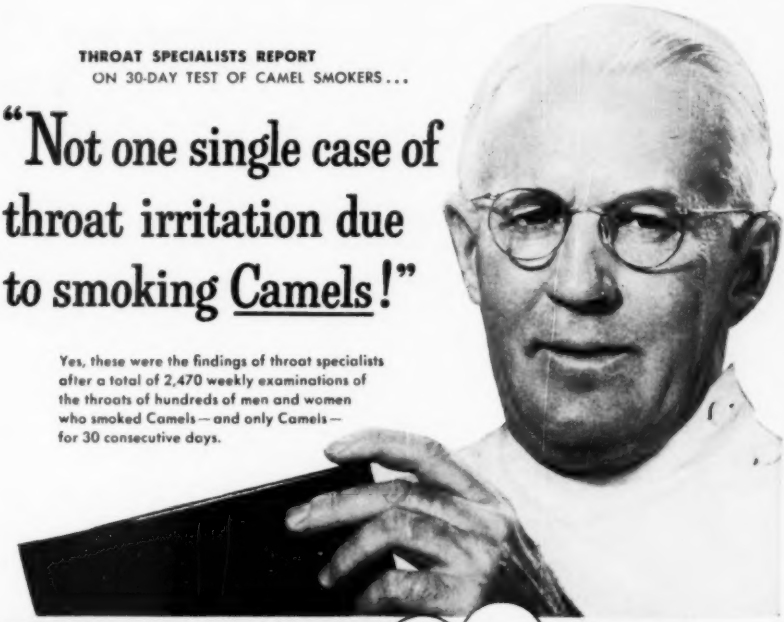

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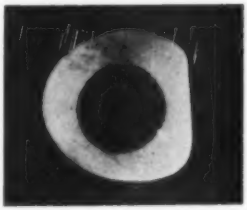

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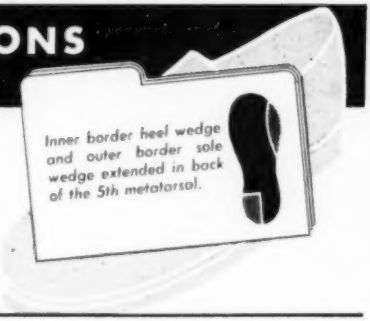

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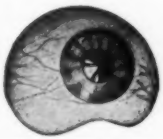

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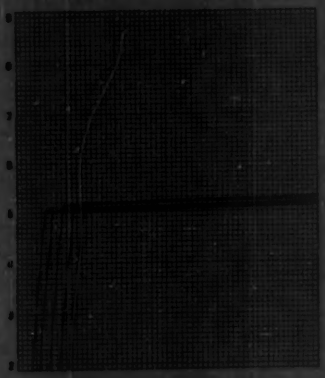

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